Small molecule inhibitors of the Mcl-1 oncoprotein based on a 1-hydroxy-2-naphthoate scaffold

Summary

Myeloid cell leukemia-1 (Mcl-1) is an oncoprotein over-expressed in multiple human cancers and is responsible for resistance to conventional anti-cancer agents. An anti-apoptotic member of the Bcl-2 protein family, Mcl-1 plays a major role in the homeostasis of cell proliferation and cell death. The cell-killing function of the pro-apoptotic Bcl-2 proteins is antagonized by the sequestration of their BH3 domains into a hydrophobic cleft on the surface of Mcl-1. Such evasion of apoptosis is a hallmark of cancer and one of the culprit for the development of resistance to current chemo- and radiotherapies. Upregulation of Mcl-1 has been directly linked to the reduced efficacy of several FDA-approved anti-cancer chemotherapies.

UMB researchers have developed small molecules that recognize this hydrophobic cleft on the surface of Mcl-1, inhibiting its anti-apoptotic function of and allowing pro-apoptotic proteins to induce cell death. Cell culture work has shown select compounds inhibit cell proliferation, as measured by a cell titer blue assay.

Key Investigator
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Field
Oncology

Technology
Mcl-1 small molecule inhibitors

Advantages
Novel, rationally-designed compounds with potential use in multiple hyperproliferative indications

Status
Available for licensing
Available for sponsored research

Patent Status
PCT Application

UMB Docket Reference
SF-2014-103

External Reference
Chen and Fletcher (2017) Expert Opin Ther Pat. 27(2):163-178.

Lanning et al. (2016) Eur J Med Chem. 113:273-292.

Market

Mcl-1 overexpression and/or amplification of the Mcl-l gene is present in many human solid tumors, including pancreatic, prostate, cervical, lung and breast cancers, as well as B-cell lymphomas and hematological cancers. While certain Bcl-$_{XL}$/Bcl-2 inhibitors have been tested in clinical trials, their low affinity for Mcl-1 is a contributing factor to the observed resistance of several tumor cell lines. The pharmacologic inhibition of Mcl-1 is an attractive, complementary, and/or adjuvant strategy towards the execution of cancer cells by re-activating apoptosis. As there are currently no Mcl-1 inhibitors in clinical trials, these novel small molecules are attractive new drug candidates for the treatment of hyperproliferative disorders.

Technology

These novel small molecule Mcl-1 inhibitors target R263 and the p2 and p3 pockets within the hydrophobic BH3-binding crevice on the surface of the protein. Compounds synthesized have a Ki of 31 nM for Mcl-1 with a specificity 11 -fold over Bcl-$_{XL}$. The two-step synthesis process allows rapid synthesis and testing of over 40 analogs, with affinities spanning over a 10,000 fold range. The structure-activity relationship analysis suggests multiple strategies to improve affinity and specificity.

Technology Status

Novel compounds have been identified using molecular modeling, SILCS structure-activity relationship (SAR) analysis and functional group mapping. Further analogues can be synthesized, with the detailed interpretation of the experimental SAR data facilitating their optimization.

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